

## **Supplementary Methods:**

### **Viral sequencing, bioinformatic analyses, and SARS-CoV-2 lineage designation**

#### **Viral sequencing**

RNA was extracted from 400 µL of remnant patient anterior nares samples using the MagMAX Viral/Pathogen kit (ThermoScientific). RNA libraries (5µL RNA input volume) were generated using the Rapid RNA Library Kit protocol (Swift Biosciences/Integrated DNA Technologies). SARS-CoV-2 genome was enriched and captured using the Respiratory Virus Research Panel hybridization probe panel (Twist Biosciences). Samples were sequenced using the NovaSeq 6000 Sequencing system S1 flow cell, with S1 Reagent Kit v1.5 (300 cycles).

#### **Bioinformatic analyses**

The flow cell output was demultiplexed with bcl2fastq (Illumina) into per-sample FASTQ sequences. These sequences were then processed using the Helix fastagenerator pipeline to produce a consensus sequence FASTA file. First, reads were aligned to a reference set consisting of a representative genome of each respiratory virus that was targeted by the hybridization probes, and the human transcriptome (GENCODE v37) using BWA-MEM. The non-human reads were then re-aligned to an expanded set of respiratory viruses reference genomes including the SARS-CoV-2 genome (NCBI accession NC\_045512.2) using a de Bruijn graph based algorithm (based on <https://doi.org/10.1093/bioinformatics/btz814>) to identify sequences that best match the reads. SARS-CoV-2 aligned reads were then marked for duplicates followed by variant

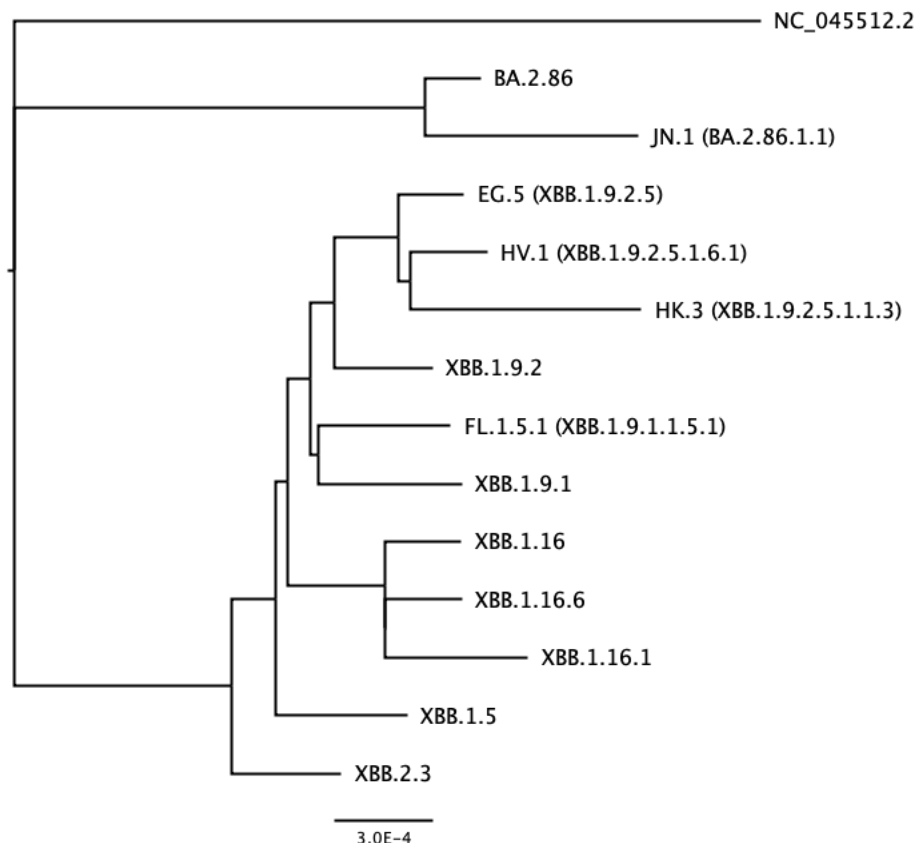
calling using the Haplotyper algorithm (Sentieon, Inc). The consensus sequence for each sample was generated from the alignment (BAM) and variant call format (VCF) files according to the following criteria: coverage from at least 5 unique reads with at least 80% of the reads supporting the call at the base position. For the bases that did not meet this criteria, an N was reported. A sequence is considered to pass quality criteria if it contains at most 30% N bases.

### **SARS-CoV-2 lineage designation**

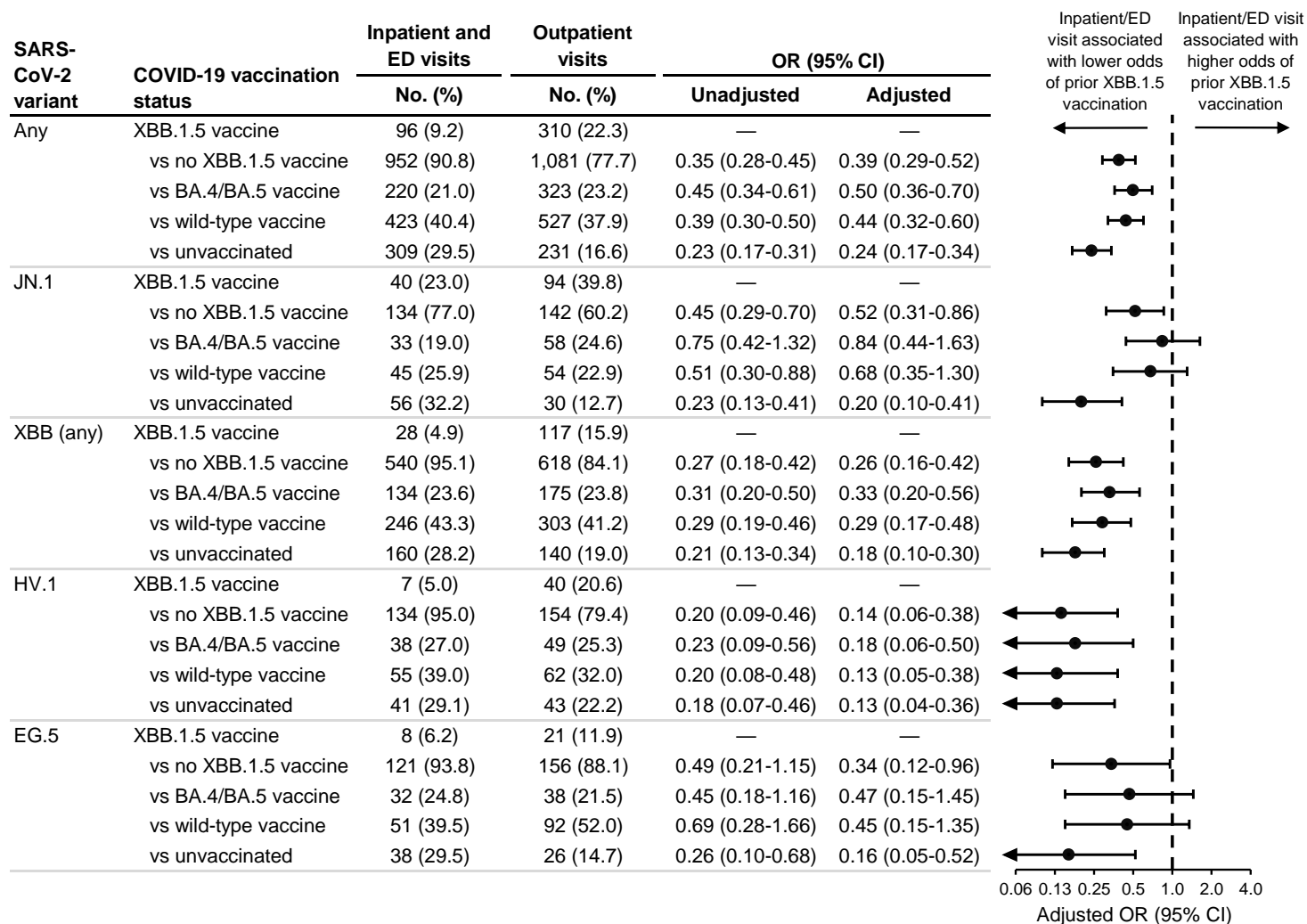
Viral sequences were assigned a PANGO lineage using pangolin (<https://github.com/cov-lineages/pangolin>). For this analysis, Pangolin data version v1.23.1 with Pangolin software v4.3.1 was used.

**Supplementary Table 1. Health Systems Participating in the ViEW Network™.**

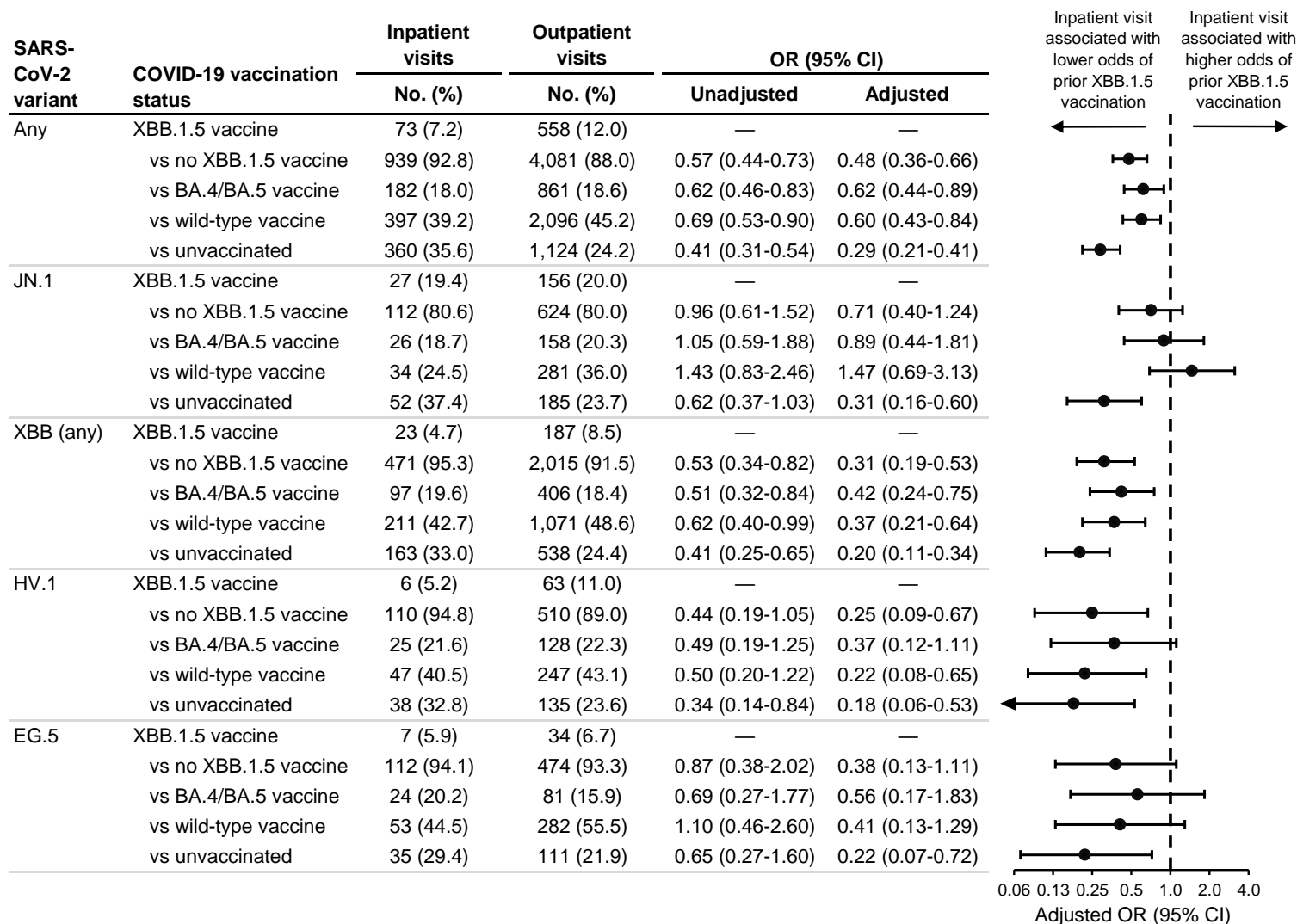
Health system	HealthPartners	Providence Health	Medical University of South Carolina
Protocol number	0006-001	0006-001	0006-001
Institutional Review Board (IRB)	WCG IRB	WCG IRB	MUSC IRB
IRB approval number	20224919	20224919	Pro00129083
Geographic region	Minnesota and western Wisconsin	Eastern Washington and southern California	South Carolina
Sample size	5,466	883	202
Date range of patients included	September 24, 2023–January 20, 2024	September 24, 2023–January 21, 2024	September 24, 2023–January 13, 2024
Vaccine record data sources	Epic electronic health record, data linkage with the Minnesota Immunization Information Connection (MIIC), and medical and pharmacy claims data	Epic electronic health record and data linkages with the California Immunization Registry (CAIR) and Washington State Immunization Information System (WAIS)	Epic electronic health record; immunization records in the South Carolina Statewide Immunization Online Network (SIMON) are reconciled in Epic after a patient's appointment
Informed consent	Waiver of consent obtained	Waiver of consent obtained	Waiver of consent obtained
Data privacy	Limited dataset stripped of direct identifiers	Limited dataset stripped of direct identifiers	Limited dataset stripped of direct identifiers



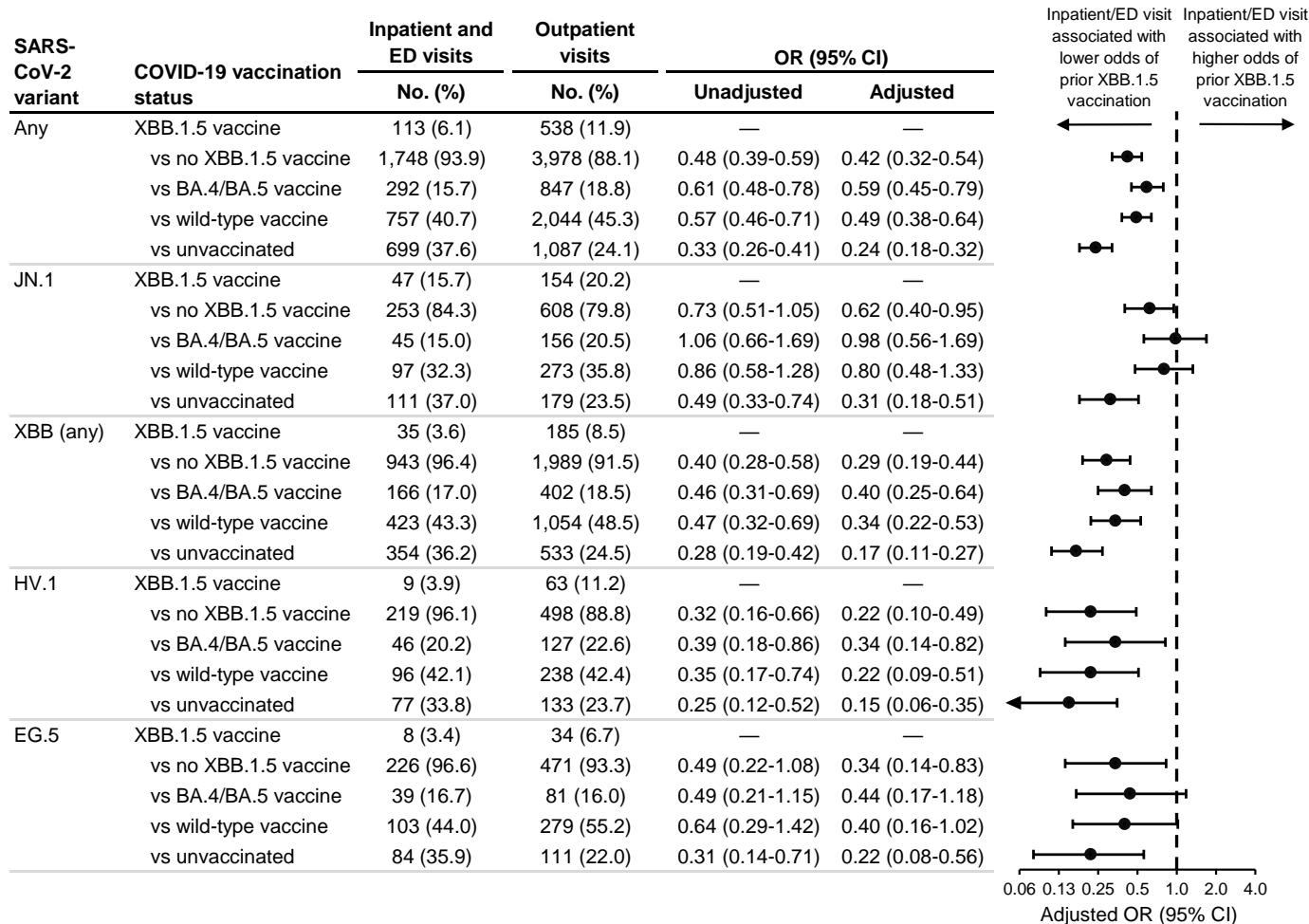
**Supplementary Figure 1. Phylogram of SARS-CoV-2 lineage categories.** The lengths of the branches are proportional to the genetic difference between variants. The distance bar shown represents 3 mutations per 10,000 bases. For each lineage, the most complete whole genome sequence from the earliest collection month associated with that lineage in our dataset was used. Sequence alignment and tree construction was carried out on the whole genome sequences using Augur, a tool developed by Nextstrain (<https://docs.nextstrain.org/projects/augur/en/stable/>). NC\_045512.2 is the accession number for the originally published sequence for SARS-CoV-2, representing PANGO lineage “B”. Except for FL.1.5.1, sublineages of XBB.1.9.1 are aggregated with XBB.1.9.1. Except for HV.1 and HK.3, sublineages of EG.5 are aggregated with EG.5. Except for EG.5, HV.1, and HK.3, sublineages of XBB.1.9.2 are aggregated with XBB.1.9.2. Except for XBB.1.16.1 and XBB.1.16.6, sublineages of XBB.1.16 are aggregated with XBB.1.16. Except for JN.1, sublineages of BA.2.86 are aggregated with BA.2.86. Sublineages of each other named lineage are aggregated with the respective lineage.



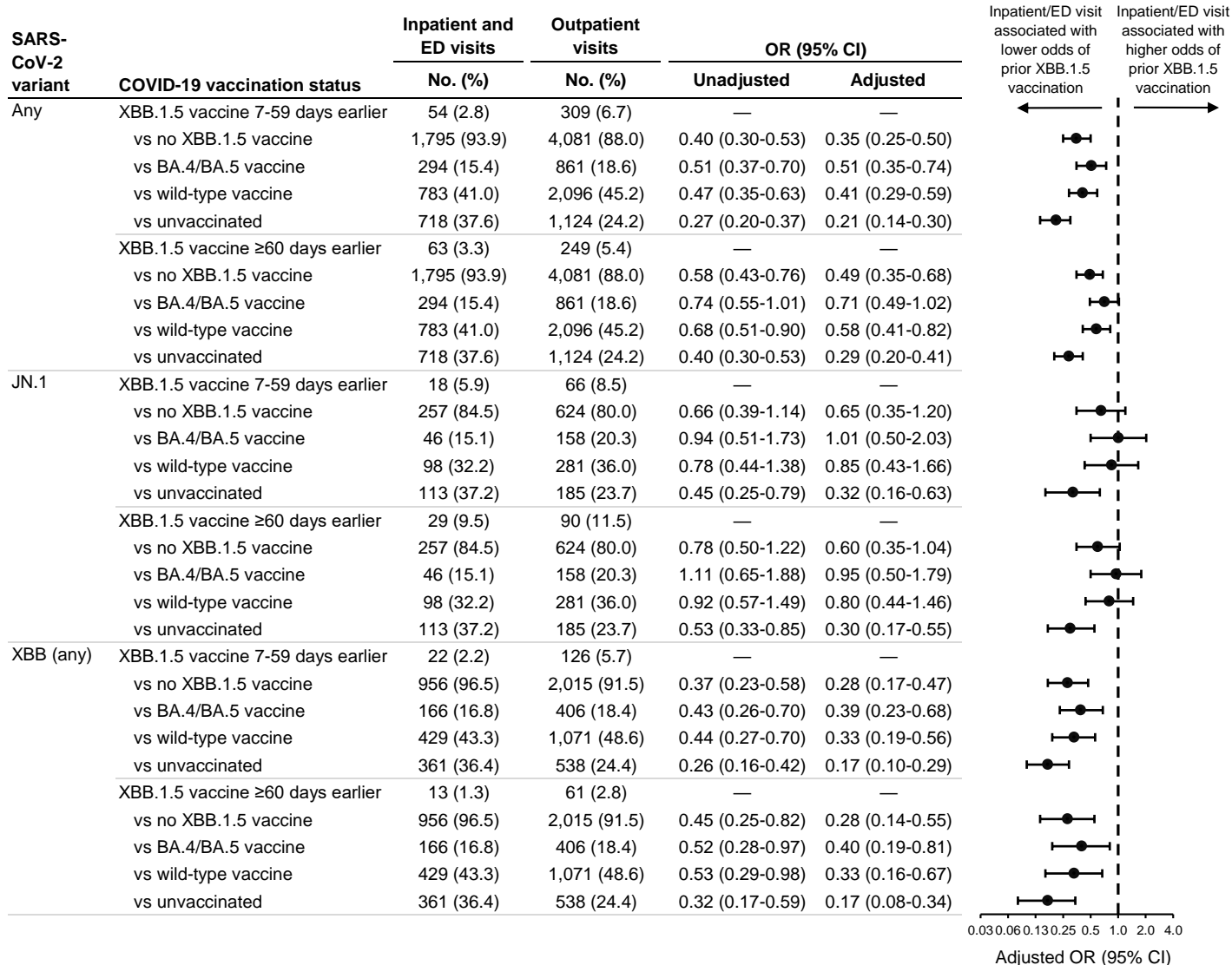
**Supplementary Figure 2. Association between inpatient or emergency department vs outpatient visit type and prior receipt of an XBB.1.5 vaccine among older adults aged  $\geq 65$  years.** Associations were calculated among all SARS-CoV-2 infections and among JN.1, XBB (any sublineage), HV.1, and EG.5 infections. Odds ratios (ORs) were calculated comparing prior receipt of an XBB.1.5 vaccine to no prior receipt of an XBB.1.5 vaccine (irrespective of previous COVID-19 vaccination history) as well as to each of three specific reference groups: 1) prior receipt of a BA.4/BA.5 vaccine but not an XBB.1.5 vaccine; 2) prior receipt of a wild-type vaccine but not a BA.4/BA.5 or XBB.1.5 vaccine; and 3) unvaccinated. Adjusted ORs were adjusted for age group (18-49, 50-64, 65-74, 75-84, and  $\geq 85$  years), sex, race and ethnicity (Asian, non-Hispanic; Black, non-Hispanic; Hispanic; white, non-Hispanic; and other/unknown), health system and state of residence, and collection date (natural cubic spline with 4 degrees of freedom). CI indicates confidence interval; ED, emergency department.



**Supplementary Figure 3. Association between inpatient vs outpatient visit type and prior receipt of an XBB.1.5 vaccine.** Associations were calculated among all SARS-CoV-2 infections and among JN.1, XBB (any sublineage), HV.1, and EG.5 infections. Odds ratios (ORs) were calculated comparing prior receipt of an XBB.1.5 vaccine to no prior receipt of an XBB.1.5 vaccine (irrespective of previous COVID-19 vaccination history) as well as to each of three specific reference groups: 1) prior receipt of a BA.4/BA.5 vaccine but not an XBB.1.5 vaccine; 2) prior receipt of a wild-type vaccine but not a BA.4/BA.5 or XBB.1.5 vaccine; and 3) unvaccinated. Adjusted ORs were adjusted for age group (18-49, 50-64, 65-74, 75-84, and  $\geq 85$  years), sex, race and ethnicity (Asian, non-Hispanic; Black, non-Hispanic; Hispanic; white, non-Hispanic; and other/unknown), health system and state of residence, and collection date (natural cubic spline with 4 degrees of freedom). CI indicates confidence interval.

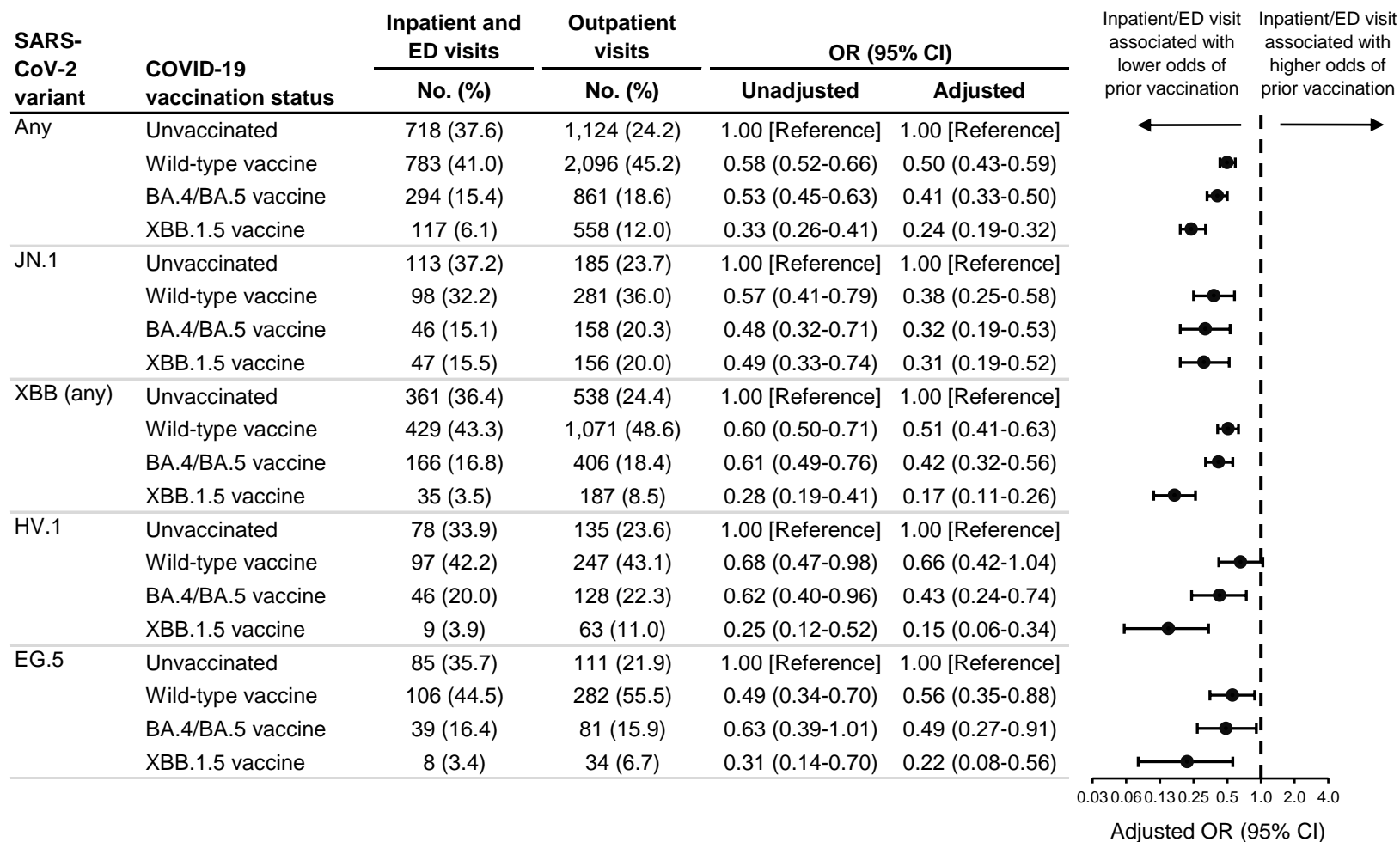


**Supplementary Figure 4. Association between inpatient or emergency department vs outpatient visit type and prior receipt of an XBB.1.5 vaccine among SARS-CoV-2 mono-infected patients.** Patients with a known respiratory virus coinfection were excluded (174), which included influenza (70), rhinovirus/enterovirus (42), RSV (28), human coronavirus (24), parainfluenza (9), adenovirus (3), human metapneumovirus (1), and bocavirus (1) coinfections. Associations were calculated among all SARS-CoV-2 infections and among JN.1, XBB (any sublineage), HV.1, and EG.5 infections. Odds ratios (ORs) were calculated comparing prior receipt of an XBB.1.5 vaccine to no prior receipt of an XBB.1.5 vaccine (irrespective of previous COVID-19 vaccination history) as well as to each of three specific reference groups: 1) prior receipt of a BA.4/BA.5 vaccine but not an XBB.1.5 vaccine; 2) prior receipt of a wild-type vaccine but not a BA.4/BA.5 or XBB.1.5 vaccine; and 3) unvaccinated. Adjusted ORs were adjusted for age group (18-49, 50-64, 65-74, 75-84, and ≥85 years), sex, race and ethnicity (Asian, non-Hispanic; Black, non-Hispanic; Hispanic; white, non-Hispanic; and other/unknown), health system and state of residence, and collection date (natural cubic spline with 4 degrees of freedom). CI indicates confidence interval; ED, emergency department.



**Supplementary Figure 5. Association between inpatient or emergency department vs outpatient visit type and prior receipt of an XBB.1.5 vaccine 7-59 and ≥60 days earlier.** Associations were calculated among all SARS-CoV-2 infections and among JN.1 and XBB (any sublineage) infections. Odds ratios (ORs) were calculated comparing both receipt of an XBB.1.5 vaccine 7-59 days earlier and receipt of an XBB.1.5 vaccine ≥60 days earlier to no prior receipt of an XBB.1.5 vaccine (irrespective of previous COVID-19 vaccination history) as well as to each of three specific reference groups: 1) prior receipt of a BA.4/BA.5 vaccine but not an XBB.1.5 vaccine; 2) prior receipt of a wild-type vaccine but not a BA.4/BA.5 or XBB.1.5 vaccine; and 3) unvaccinated. Adjusted ORs were adjusted for age group (18-49, 50-64, 65-74, 75-84, and ≥85 years), sex, race and ethnicity (Asian, non-Hispanic; Black, non-Hispanic; Hispanic; white, non-Hispanic; and other/unknown), health system and state of residence, and collection date (natural cubic spline with 4 degrees of freedom). CI indicates confidence interval; ED, emergency department.





**Supplementary Figure 6. Association between inpatient or emergency department vs outpatient visit type and prior receipt of a wild-type, BA.4/BA.5, or XBB.1.5 vaccine, each vs unvaccinated.** Associations were calculated among all SARS-CoV-2 infections and among JN.1, XBB (any sublineage), HV.1, and EG.5 infections. Odds ratios (ORs) were calculated comparing each of three groups to unvaccinated: 1) prior receipt of a wild-type vaccine but not a BA.4/BA.5 or XBB.1.5 vaccine; 2) prior receipt of a BA.4/BA.5 vaccine but not an XBB.1.5 vaccine; and 3) prior receipt of an XBB.1.5 vaccine. Adjusted ORs were adjusted for age group (18-49, 50-64, 65-74, 75-84, and  $\geq 85$  years), sex, race and ethnicity (Asian, non-Hispanic; Black, non-Hispanic; Hispanic; white, non-Hispanic; and other/unknown), health system and state of residence, and collection date (natural cubic spline with 4 degrees of freedom). CI indicates confidence interval; ED, emergency department.